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ABSTRACT

The toxic effects of lead, a useful metal ubiquitous in the human environment, have long been known. The occupational hazards of lead poisoning were well established by the early 19th century, but plumbism in children caused by paint ingestion was not reported until the turn of the century. Even in 1924, the child was said to live in a "lead world." Despite its preventable nature and formidable mortality and morbidity rates, only in the late 1960s did childhood lead poisoning gain general recognition as an important public health problem in the United States. Federally-funded projects began mass screening of children for lead poisoning in July 1971. As of March 31, 1975, approximately 980,000 children had been screened in these projects. Sixty thousand had blood lead levels of 40 micrograms/100 milliliters or more confirmed on retesting; 10,300 received chelation therapy. Thousands of children with elevated blood levels did not return for retesting and followup. Recent data indicate that lead poisoning and undue lead absorption in children are widespread phenomena not limited to older sections of the inner cities. Aside from lead paint, other potentially hazardous sources include dust, dirt, air, and miscellaneous items. Undue lead absorption without overt clinical toxicity may be associated with psychological and other impairments. (Author/SS)

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UNDUE LEAD ABSORPTION AND LEAD POISONING IN CHILDREN—AN OVERVIEW

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ABSTRACT

The toxic effects of lead, a useful metal ubiquitous in man's environment, have long been known. The occupational hazards of lead poisoning were well established by the early 19th century, but plumbism in children caused by paint ingestion was not reported until the turn of the century. Even in 1924, the child was said to live in a "lead world." Despite its preventable nature and formidable mortality and morbidity rates, only in the late 1960's did childhood lead poisoning gain general recognition as an important public health problem in the United States. Federally-funded projects began mass screening of children for lead poisoning in July 1971. As of March 31, 1975, approximately 980,000 children had been screened in these projects. Sixty thousand had blood lead levels of 40 micrograms/100 milliliters or more confirmed on retesting; 10,300 received chelation therapy. Thousands of children with elevated blood levels did not return for retesting and followup. Recent data indicate that lead poisoning and undue lead absorption in children are widespread phenomena not limited to older sections of the inner cities. Aside from lead paint, other potentially hazardous sources include dust, dirt, air, and miscellaneous items. Undue lead absorption without overt clinical toxicity may be associated with psychological and other impairments.

RÉSUMÉ

Les effets toxiques du plomb, métal utilisé partout dans l'environnement humain, sont connus depuis longtemps. Les maladies industrielles dues au plomb ont été décrites au début du XIX^{e} s., mais ce n'est qu'au tournant du XX^{e} qu'on a signalé chez les enfants le saturnisme dû à l'ingestion de peinture. Déjà en 1924, on disait que l'enfant vivait dans "un monde de plomb". Ce n'est qu'à la fin des années 60 que l'on reconnut unanimement le grave danger que représente l'empoisonnement par le plomb chez les enfants, aux États-Unis. Des études financées par le gouvernement fédéral et visant au dépistage systématique des enfants empoisonnés ont débuté en juillet 1971. A la date du 31 mars 1975, 980 000 enfants environ avaient été analysés. Parmi eux, 60 000 avaient des taux

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de 40 μg/100 ml ou plus (confirmés ou sujets à de nouveaux tests); 10 300 ont reçu le traitement par chélation. Des milliers d'enfants à plombémie élevé ne sont pas revenus pour de nouveaux tests ou des soins. Les résultats récents indiquent que l'empoisonnement par le plomb et la forte plombémie sont répandus chez les enfants et ne se confinent pas aux vieux quartiers des villes. Outre la peinture à base de plomb, la poussière, la saleté et l'air peuvent être dangereux. La plombémie subclinique pourrait entrainer des handicaps psychologiques et autres.

INTRODUCTION

Lead is a useful trace element ubiquitous in man's environment. Mining and processing of this valuable metal began early in man's civilization and its use by the Greeks and Romans is well known. The toxic effects of lead have also long been recognized. Although Hippocrates is frequently cited as the first to recognize lead as a cause of clinical illness, this statement has been seriously questioned, and the first definite clinical account of lead poisoning should perhaps be accredited to Nicander, the Greek poet-physician who in the second century B.C. described several classical signs and symptoms of lead poisoning such as constipation, abdominal pain, pallor and palsy in men following ingestion of litharge (lead monoxide) and cerusse (lead carbonate). (1) The noted physician, botanist, and pharmacologist Dioscorides observed in the first century A.D. that colic and paralysis followed both ingestion of lead and inhalation of its fumes, and thereby identified the two major routes of absorption of this toxic element. (2)

Over the centuries, lead contaminated food and drink have been linked to a number of outbreaks of colic. These are known variously as the colic of Poitou of France, the entrapado of Spain, the Huttenkatze of Germany, the dry bellyache of America, the bellain of Derbyshire, and the colic of Devonshire of England. (1) With industrialization and ever wider application of this useful but toxic metal, occupational lead poisoning became an increasingly important problem. By the early 19th century, lead poisoning as an occupational disease was well established, but meaningful improvement in industrial hygienic standards was not instituted until several decades later. Since the early 1900's, there has been a significant reduction in the occurrence of severe occupational lead poisoning. (2,3) Today, estimates of the magnitude of this industrial problem are fragmentary, but lead poisoning was recently cited to be the most common notifiable industrial disease in Great Britain. (4)

HISTORICAL PERSPECTIVE ON LEAD POISONING IN CHILDREN

Lead poisoning in children occupies a unique position in the history of modern medicine, for few preventable childhood illnesses with such high mortality and morbidity have been so seriously neglected for so long. Preventive medicine has made advances such as development of vaccines for many infections, and prenatal diagnosis of genetic disorders, but has done virtually nothing for this severely crippling and often fatal disease.

Congenital Lead Poisoning

Before the turn of the century, this illness was largely reported as occurring among children of lead workers, and was referred to as "congenital" or "hereditary" lead poisoning. A high incidence of sterility, stillbirth and abortion was observed not only in women occupationally exposed to lead, but also among those married to lead workers. Convulsions, retarded growth and development, macrocephaly and other malformations of the head were frequently reported in children born alive. (3,5) As late as 1930, infant mortality among offspring of parents occupationally exposed to lead was reported to be more than twice the national average for Italy. (3) These early observations are of particular interest in view of the recent report that moderately increased lead absorption among men occupationally exposed is associated with an increased frequency of asthenospermia, hypospermia and teratospermia. (6) But with greater awareness of this occupational hazard in recent decades, overt lead poisoning in children caused by parental exposure has become a rare entity. However, occasional cases of congenital lead poisoning attributed to ingestion of "moonshine" whiskey by pregnant women and other causes have been reported. (7,8)

Lead Paint Poisoning in Australia

In 1892, Gibson *et al.* first called attention to an unexplained prevalence of lead poisoning among children in Brisbane, Australia. (9) But it was not until 1904 that Gibson identified lead paint on houses as the major source of the poisoning in children. He also noted the danger of lead-containing house dust and reported that one sample of dust weighing 0.2 gm had a lead carbonate content of 1.5 mg. He further observed that hand-to-mouth activities in children. such as nail biting and thumb sucking, were responsible

for introducing this toxic substance into the body and noted that this illness was clearly preventable. (10)

This epoch-making paper was received with mixed acceptance and skepticism, and for a number of years lead paint poisoning was thought by some to be a problem peculiar to children in Australia. Only scattered reports of lead "meningitis" appeared in the literature during this period, many traced to chewing of lead paint from cribs or other furniture. (11-14)

The Child in a "Lead World" in 1924

In 1924, Ruddock observed that mild cases of lead poisoning in children were quite common in the United States, and called attention to the fact that pica, or perverted appetite for non-food items, was an important etiologic factor. In addition to lead paint, he cited other sources of poisoning such as lead chromate in food coloring, lead food receptacles, and lead medicinal ointments, and observed that the child "lives in a lead world." (15) Following Ruddock's paper, several reports indicated that lead poisoning was a common pediatric problem, but they attracted little attention. In 1932, McKhann reported forty cases seen at the Boston Infant's and Children's Hospital in the previous six years; 9 of these children died. (16)

The "Depression Disease" caused by Burning Battery Casings

At about this time, temporary diversion of attention from lead paint followed reports from Baltimore of mass lead poisoning in poor families during the depression years caused by burning discarded storage battery casings for fuel in cold weather. Forty cases, mostly children, were identified in that city in 1932. These outbreaks of lead poisoning, dubbed then as the "depression disease" served to focus some attention on the problem. When halting the burning of battery casings failed to eliminate lead poisoning in children, some health workers did become aware of the etiologic role played by lead paint as well as the prevalence of this public health problem. (17,18,19)

Lead Paint Poisoning–1930's to 1960's

Between the 1930's and 1960's alert workers in some U.S. cities made limited attempts to deal with the problem. Invariably, increased awareness among health workers was associated with an increase in the number of reported cases and a decrease in severe cases and fatalities. Data published

during this period clearly indicated that lead poisoning in children, caused largely by repeated ingestion of lead paint in dilapidated housing, was a major public health problem. Hundreds of cases with scores of deaths from lead poisoning were reported. (20-29) Even after the introduction of BAL and Ca EDTA as chelating agents in the 1950's, the fatality rate in children treated for lead encephalopathy remained between 25-30% for many years. (26,28) It was not until 1966 that a rate of less than 5% was first reported. (29)

The literature published between the 1930's and 1960's further indicated an extremely poor outlook for children who survived. A study of 425 children conducted 6 months to 10 years after treatment for lead poisoning revealed that 39% had some kind of neurological sequela. Among children who presented with encephalopathy initially, 82% were left with handicaps: 54% had recurrent convulsive seizures, 38% were mentally retarded, 13% had cerebral palsy, and 6% had optic atrophy. Even among children who were thought to be without symptoms at the time of diagnosis, 9% were found to be mentally retarded at follow-up. (30) Several other studies of children with milder forms of lead poisoning indicated that deficits in visuomotor functions and behavioral disorders such as short attention span, restlessness, easy distractibility, and impulsiveness were common. In spite of adequate intelligence, many children did poorly in school. (25,31-35)

The problem was not unique to the U.S. In 1935, Ross and Brown reported that in the previous two years, 23 cases of lead poisoning were treated at the Hospital for Sick Children in Toronto; 5 of these children died. These investigators stated that lead poisoning was probably "the most common single cause of poisoning in children." (36) Between 1948 and 1967, lead poisoning was diagnosed in 90 children at two hospitals in Sydney, Australia. Kramer *et al.* reported 22 cases from Germany in 1962. (37,38)

Reasons for Inaction

Surprisingly, the public was, in general, unaware of the existence of the problem at that time. A number of factors probably contributed to this.

In the early 1940's, when titanium oxide began to replace lead pigment in interior paints, many erroneously thought that the problem of lead paint poisoning in children was solved. They did not realize that millions of houses were covered with layers of old lead paint, and that exterior paint was among the sources of lead poisoning which posed a definite hazard. Moreover, it was not until 1955 that a voluntary standard of limiting lead in interior paint to 1% was adopted. (39)

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Non-specificity of the symptoms of lead poisoning in children further confounded the problem. Irritability, apathy, anemia, anorexia, abdominal pain, vomiting, constipation, developmental delays or regression, and even convulsions may all be misinterpreted as indications of other childhood illnesses. Moreover, epidemiological data available then indicated that the problem was almost strictly confined to the poor, for high risk areas were synonymous with inner city slums. In short, childhood lead poisoning was considered by many to be a health problem inextricably associated with poverty for which little could be done. (20-28,39,40)

General Awakening to a Public Health Problem

In the mid-to-late 1960's, concomitant with an awakening of social conscience, came the realization that lead poisoning, long known to be a preventable cause of death and serious handicaps in children, and thought by many to be a disease of the past, was still very common in the U.S.

The Children's Bureau in the Department of Health, Education, and Welfare together with many other public agencies and private institutions exerted considerable efforts at educating not only the general public, but physicians and other health workers as well to the continuing hazard. (39-45) Several large cities, led by Chicago, began or expanded existing case-finding efforts into mass screening programs. Between 1967 and 1970, several large U.S. cities reported that 25-45% of children 1-6 years old tested, living in old deteriorating neighborhoods, had blood lead levels that exceeded 40 μg/100 ml of whole blood, the upper limit of normal. (40,46-49) And for the first time, undue lead absorption unassociated with overt clinical evidence of toxicity was recognized as a phenomenon which required careful investigation because of the enormous number of young children involved. (40) Although it is not known what fraction of these children were later confirmed to have elevated blood lead levels, the magnitude of the problem was indicated by the fact that in 1967 and 1968, 1,155 children were treated for lead poisoning in Chicago. (47)

RECENT DEVELOPMENTS

Mass Screening—From Treatment to Prevention

In 1970, the U.S. Surgeon General issued a statement which shifted focus on the problem from case finding and treatment of actual lead

poisoning to its prevention through mass screening and early termination of hazardous exposure for those with evidence of undue lead absorption. (40,50) The 1971 Lead-Based Paint Poisoning Prevention Act followed, which authorized Federal financial assistance to help communities develop and carry out screening and treatment programs and to eliminate the cause of lead paint poisoning. (51) Beginning in July of the same year, provisions of the Act calling for mass screening of children were put into effect. Forty projects were funded by the Department of Health, Education, and Welfare in the first fiscal year (FY) and the number of projects has since increased to 77. Data for the first FY are not available, but for the FYs 73, 74, 75, a total of 1,002,360 children were screened; of these 64,385 or 6.42% were found to have blood lead levels of 40 μg/100 ml. or more which were confirmed on subsequent testing. Of these, 10,235 children were chelated for lead poisoning. However, a substantial number of children initially found to have elevated blood lead levels did not return for further testing. In FY 73, 24% or over 8,000 children, and in FY 74, 14% or 4,200 children whose screening showed elevated blood lead levels did not return for confirmatory tests. (52-56) These recent figures reflect a lower but still significant prevalence of undue lead absorption among children. Increased community awareness and some attempts at controlling lead hazards must have contributed to this decrease, but the most important factor probably was that earlier screening programs were aimed almost exclusively at children at highest risk. More recently, screening programs have included a wider geographic area and children at lower risk. A few exploratory projects yielded minimum positive findings, while others continued to report a significant prevalence. For example, from 7/1/72 to 6/30/73, a total of 277,346 children were screened in these projects of whom 7.17% had confirmed blood lead levels of 40 μg/100 ml; 1.2% were treated for lead poisoning. In the same period, such blood lead levels were found in 30.8% of 5,731 children screened in Milwaukee, and 19% of 2,885 children screened in Erie County, New York. Of the children screened, 9.8% and 7.6% respectively were treated for lead poisoning in these areas. (52,53)

In 1971, a Department of Health, Education, and Welfare ad hoc committee established that 300 micrograms of elemental lead is the maximum daily permissible intake (DPI) from all sources for children 1-3 years old. (57)

Recent Epidemiological Data

Unitl the late 1960's, epidemiological data indicated that lead poisoning was found almost exclusively among children 1-6 years old living in dilapidated houses with peeling lead paint in large inner cities. Common

occurrence of pica and ready access to lead paint provided an optimum environment for poisoning. A higher prevalence in the blacks was attributed to the fact that a greater proportion of this population lived in the so-called "lead-belts". Also, more cases occurred in the summer. (39) Data collected since then have changed the picture somewhat.

Although young children with pica residing in poorly maintained old houses in inner cities are still at greatest risk, there are now indications that lead poisoning and undue lead absorption, particularly the latter, are not confined to the poor living in the inner cities.

As screening programs began to cover areas not conventionally thought of as "lead belts," the previously well defined boundaries of these areas began to disappear. In some areas, close to 50% of the cases came from outside of the inner city. Nor is the problem confined to large urban areas. (58) Between 1971 and 1973, the Department of Health, Education, and Welfare conducted limited surveys in 58 communities representing diverse geographic areas and ranging in size from 5,000 to 100,000 in population. The findings indicated that undue lead absorption among children is a geographically widespread phenomenon found in smaller communities as well. (58,59) Recent data submitted by the 77 projects funded by the Department give further evidence that the problem exists in all regions of the country, but the prevalence varies. (52-56) Even children in rural areas are not spared, although the prevalence is lower. In one survey, 9% of 230 rural children and 23% of 272 urban children were found to have elevated blood lead levels, several coming from middle and upper middle class homes. (60) Among children from comparable socio-economic and housing backgrounds, black children have a higher prevalence than non-blacks. In cities with similar housing problems, the prevalence of lead poisoning also varies considerably, indicating that there are other contributing factors. (59,61) Not only is clinical lead poisoning more common in the summer, but blood lead levels also fluctuate with season. (46)

Until the late 1960's, reports indicated that with rare exceptions, lead poisoning in children resulted almost exclusively from ingestion of lead paint on houses. (22-27,39) As the focus on the problem broadened to include not only children with overt lead poisoning but also those with evidence of undue lead absorption, it became obvious that lead paint on houses and a history of pica could not always be identified, particularly among children with mild to moderately elevated blood lead levels. Milwaukee recently reported that of 1,314 housing units where children with lead poisoning resided, a lead paint hazard was found in only 63%. (62) One percent lead in paint, a limit often used in housing inspections, is no longer considered safe. (63) Nor should negative housing inspection or history of ingestion be interpreted as

incontrovertible evidence that paint is not the cause, but other sources should also be investigated. Moreover, among children known to ingest paint, contribution by other hazardous sources cannot be ruled out.

THE LEAD WORLD TODAY

As the perspective on hazardous lead sources has broadened, it has become obvious that 50 years after Ruddock said that the child lives in a lead world, (15) the statement is still true in many areas, though the sources may have changed somewhat. For, in addition to some degree of exposure through food, drink and air which is inevitable, there are also many potentially dangerous sources.

Lead Paint on Houses

Today, seven decades after lead paint was recognized as a cause of severe lead poisoning in children, there are an estimated forty million housing units in the U.S. built prior to 1950 which are potential sources of lead paint poisoning. Five to seven million of these units are considered immediate hazards because of the poor state of maintenance. (64)

Lead in Air, Dust, Dirt, and Soil

The possible contribution of airborne lead from auto exhaust and industrial sources to body lead burden has attracted considerable attention in recent years. Epidemiologic studies of blood lead level in general and occupational groups have shown a logarithmic regression on estimated atmospheric exposure. (65) Studies in adults and children have further demonstrated that the mean blood lead levels of urban populations are significantly higher than those of suburban or rural populations. (40,60,66,67)

One recent study reported that children living within 100 feet of major urban roadways have a significantly higher frequency of elevated blood lead levels than those living farther away. Among children living within 200 feet of a major artery, those from areas with greater traffic densities have a higher frequency of elevated blood lead levels than those in areas with less traffic. (68)

However, other investigators have reported that blood lead levels in the general population and body tissue lead content measured postmortem have not changed significantly since the introduction of leaded gasoline. (69, 70)

There is increasing evidence that lead in dust and dirt is an important source of exposure in children, but the interest in the lead content of street dirt is not exactly a recent one. A limited study of street dirt in New York City in 1924 before tetraethyl lead gasoline was introduced and then ten years later indicated an average increase of about 50% in lead content of the latter specimen. The highest value encountered was 3080 ppm. (71) This compares with a 1972 report of 12,820 ppm lead in street dirt collected from a busy downtown intersection in Washington, D.C., and 4-8,000 ppm from other sites. (57) Between 1935 and 1972, the consumption of lead as a gasoline additive increased from 37,000 tons to 278,340 tons. (72,73)

Lead contaminated house dust, which Gibson recognized in 1904 as a potentially dangerous source of intake among children, (10) has only recently been rediscovered. (57,74,75) Flaking paint on houses can contaminate house dust as well as yard or garden soil; (76) however, one study of urban homes showed no difference between the lead content of house dust in homes with peeling lead paint and those negative on inspection, suggesting that flaking paint is unlikely to be the sole source of lead contamination in urban homes. (74) House dust in urban homes has been reported to have a higher lead content than that in suburban homes in some studies. (74,75) One study reported a mean lead content of urban house dust of 11,000 μg/g. (77) Others did not find such a difference but reported a higher lead content of soil around urban homes and dirt brought into the houses. (78) House dust from homes close to roadways is reported to have a higher lead content than from homes farther away. A very high lead content was recently reported in house dust and outside dirt collected from areas close to lead smelters, foundries and processing plants. The level of lead content decreased rapidly with distance from the source. (79) Within 1.6 km of a smelter, Landrigan *et al.* reported that house dust lead content ranged from 2,800 to 103,750 ppm with a geometric mean of 22,191 ppm. (80)

The bioavailability of lead in dirt, dust and soil has been a topic of considerable discussion. Of particular concern is the widespread distribution of these lead sources in many urban and industrial areas, and the proportionately greater surface areas of these small particles relative to their mass, as compared to paint chips, which may facilitate absorption. (81) Sayre *et al.* reported that not only is lead content higher in urban house dust than in suburban house dust, but hands of inner-city children also have greater amounts of lead than those of suburban children. (74) Lepow *et al.* found a mean lead concentration of 2,400 μg/g of dirt on urban children's hands. (77) This suggests that hand-to-mouth activities in some children could easily

introduce substantial amounts of lead into the body. A highly significant relationship ($p. < .0001$) between lead content of house dust and blood lead levels of children has in fact been demonstrated. (80) Needleman *et al.* reported increased dentine lead content among children in an area of industrial lead contamination where high lead contents in interior dust as well as playground dirt and gutter dirt were found. (82) Ter Haar, on the other hand, found that dust and dirt particulate did not contribute to the elevated body lead burden in a small group of children studied. (76)

Compared to house dust, a lesser but nonetheless significant relationship ($p. < 0.05$) between soil lead content and blood lead levels in children was found by Landrigan *et al.* (80) This suggests that lead in soil is less readily available to children, but Angle *et al.* found that blood lead levels in urban children correlated with lead content of yard soil and exterior dirt brought into the house. (78) Barltrop *et al.* also reported a significant difference in the blood and hair lead contents (within the normal range) of children exposed to 500 ppm and to 10,000 ppm soil lead, but concluded that such an increase in absorption is unlikely to be of biological significance. (83) Beyond the immediate danger of ingestion by children, however, lies the possibility of contamination of vegetation, forage grass and the food chain which may eventually enter the human body. (84,85)

Miscellaneous Lead Sources

The ubiquity of lead in our modern world is further illustrated by the numerous reports in recent years of a number of potentially hazardous sources such as improperly glazed earthenware and dinnerware, silver holloware, electric teakettle, color ink used in some newspapers and children's books, cosmetic products, food, milk and juices in lead soldered cans, certain toothpastes, lead core in candlewick, wrappers of specialty food, etc. (86-97). A report during the recent energy crisis of increased lead absorption in a child exposed to fumes produced by burning lead-painted wood is reminiscent of the mass poisoning during the depression years caused by burning battery casing for fuel. (17,98) The report published this year from Glasgow suggesting that chronic low level lead contamination of water may be an etiologic factor in mental retardation further brings to mind the exposure of the Romans and Greeks to this toxic metal through their elaborate lead water-carrying system. (1,99)

VULNERABILITY OF CHILDREN

Undue exposure to lead is undesirable for all, but is particularly dangerous for children for several reasons. Certain lead sources such as paint chips, and newspaper printed with lead ink do not present any problem in adults, but can be hazardous to children with pica. The high lead content of dust and dirt poses a further problem for those with normal hand-to-mouth activities. (58,74,75,77) Lead content in ambient air is greater at the height at which young children breath. (100) Higher metabolic rate and greater physical activity of children also mean that under comparable exposure, children inhale two to three times as much of a given pollutant per unit of body weight as do adults. (72,100) Recent studies further indicate a greater rate of gastrointestinal absorption and body retention of lead in young children than in adults. Alexander *et al.* report that in a group of children 3 months to 8½ years old, 53% of lead ingested was absorbed and 18% retained. (101) Compared to adults, a smaller proportion of the body lead burden is found in the bones of young children, leaving a larger pool of mobile lead in the soft tissues. (58,70) A number of nutritional factors such as iron, calcium and protein deficiency shown to potentiate lead toxicity may occur more frequently in children. (58,102-106) Finally, the immature organism with its relatively inefficient metabolism, excretory pathways, and immunological system, may be intrinsically more vulnerable to lead toxicity. (57)

TOXIC EFFECTS OF LEAD

In Humans

The toxic effects of lead on the biosynthesis of heme, central and peripheral nervous system, and kidney are well known and need no further elaboration. (72, 107) Many studies of its effects at the cellular level have also been published. (72,108) The many indices of metabolic alteration due to lead such as decrease in erythrocyte ALA-D, increase in erythrocyte protoporphyrin, serum and urinary ALA, and urinary coproporphyrin have been useful in monitoring adult occupational lead exposure and screening children for undue lead absorption. Of these, decreased ALA-D and increased erythrocyte protoporphyrin are the earliest indications. (72,109-112) A close negative correlation is found between blood lead concentrations ranging from 5 to 95 μg/100 ml and the logarithm of erythrocyte ALA-D. (110) Although the health implication of this *in vitro* effect of lead has been questioned, it

has been demonstrated recently that a direct correlation exists between erythrocyte ALA-D and ALA-D activity of liver tissue obtained on biopsy. (113)

Less well understood but nevertheless important are scattered reports of other toxic effects of lead in man such as impaired function of thyroid, pituitary-adrenal axis, myocardium, and reproductive system; chromosomal damage; defective *alpha* and *beta* globin synthesis, and bone marrow hypoplasia. (72)

In Experimental Animals

Experimental data in lower animals further suggest other detrimental effects, including teratogenicity in golden hamsters and chick embryos, carcinogenicity in rats and mice, decreased resistance to bacterial infection in mice and to bacterial endotoxin in rats, aggravation of viral disease in mice probably through reduced interferon synthesis, impaired protein synthesis in rabbits, delayed sexual development in rats and decrease in life span and breeding potential in rats and mice. (72, 114-117)

EFFECTS OF LOW LEVEL LEAD ABSORPTION

In Children

Of greater concern to many than these laboratory animal data, are the several reports published in recent years on the "subclinical" effects of lead in children without overt evidence of lead poisoning. Interest in this area intensified following discovery in the late 1960's that undue lead absorption in children is a markedly prevalent phenomenon with widespread geographic distribution. With expanding screening programs, it became apparent that the majority of the children found to have evidence of undue lead absorption did not meet current diagnostic criteria for lead poisoning and received no therapy. For the thousands and thousands of such children uncovered by screening programs each year, a crucial question remains unanswered: Does a slight but sustained increased absorption of lead cause permanent or significant impairment even in the absence of overt clinical evidence of toxicity?

It is well known that metabolic disturbances due to lead such as decreased ALA-D and increased erythrocyte protoporphyrin generally precede

clinical manifestation of poisoning. (40,72) But increasingly, reports are suggesting that psychological and other functional impairment can occur in young children with evidence of undue lead absorption who are otherwise "asymptomatic". It is essential to recognize, of course, that symptoms of lead poisoning in children such as irritability, loss of appetite, sleep disturbances, abdominal pain, apathy and vomiting, are non-specific and difficult to interpret. Manifestations typical of lead poisoning in adults such as blue gum line and peripheral nerve palsy are rarely seen in children. Early manifestations of central nervous system involvement such as behavioral changes and developmental delays or regressions are often overlooked or misinterpreted. They are recognized only in retrospect, after frank evidence of encephalopathy has set in. Some parents have reported improved behavior and language ability in children with "asymptomatic" lead poisoning following chelation. (47,58)

Although the focus on the so-called "subclinical" effect of lead in children has been a relatively recent one, even in 1943, Byers and Lord called attention to the fact that young children with lead poisoning who presented no evidence of central nervous system involvement initially, often later showed visuomotor impairment in dealing with shape, direction, space and projected imagery. Behavior disorders typical of minimal brain damage or dysfunction were common. Despite adequate intelligence, many were severely handicapped educationally. (31) These observations have since been confirmed by many others, who also observed frequent language and speech impairments in these children. (33-35)

Within the past 5 years, a number of studies have suggested that among children with undue lead absorption without overt clinical evidence of lead poisoning, behavior disorders as well as neurological and psychological impairment are common. Pueschel *et al.* reported minor neurological dysfunction and motor impairment in 22-27% of children with increased lead burden, most of whom had no major complaints suggestive of lead poisoning. (118) De la Burde compared children who had "asymptomatic" lead exposure between 1 and 3 years of age with matched controls and found that the former had a greater frequency of deficits in global IQ and associative abilities, in visual and fine motor coordination, and in behavior. At age 7 years, school failure due to learning and behavior problems was more frequent in lead exposed children than in controls. (119,120) David *et al.* reported higher blood lead levels and post-penicillamine urinary lead level in hyperactive children as compared to a control group. (121) Baloh (122) and Roberts *et al.* (79) similarly found increased incidence of hyperactivity in "asymptomatic" children with chronic increased lead absorption. Silbergeld *et*

al. demonstrated increased urinary levels of catecholamine metabolites in children with blood lead levels ranging from 58 to 69 μg/100 ml, thereby providing clues to the neurochemical alteration in lead-induced "minimal brain dysfunction hyperkinesis." (123) Landrigan *et al.* studied children with a history of chronic exposure and blood lead levels of over 40 μg/100 ml (range 40-68 μg/100 ml, mean 49), and found a significantly slower finger-wrist tapping in the dominant hand, and lower performance IQ when compared to a group of controls. (124) Perino *et al.* compared a group of black preschool children with blood lead levels of 40-70 μg/100 ml with a group of matched controls and found that as lead level increased, general cognitive, verbal and perceptual abilities decreased, suggesting that undue lead absorption may contribute to learning disabilities in young children. (125) Decreased peripheral nerve conduction velocity has been reported in both children and adults who have been unduly exposed to lead but who had no clinical evidence of peripheral neuropathy. (4,126,127)

In contrast to these findings, several studies reported negative results. Kotok has demonstrated deficiencies in fine motor adaptive and language functions in children with moderately elevated blood lead levels as well as in controls from similar socio-economic backgrounds, and concluded that such deficiencies were directly related to inadequacies in the children's environment. (128) Lansdown *et al.* found that distance from a lead pollution source was related to blood lead levels, but could not demonstrate any relationship between blood lead levels and mental function. (129) Alexander similarly reported negative findings in a group of children residing close to a lead pollution source. (130) Albert *et al.* reported that in the absence of diagnosed lead poisoning or elevated blood lead levels, excess lead exposure measured in terms of high dentine lead levels was not associated with deleterious health effects. (131) McNeil *et al.* reported negative findings in "asymptomatic" children with elevated blood lead levels living close to a smelter. (132)

Some of the above studies lack adequate controls; others use a single blood lead level as an index of undue lead absorption without consideration of the duration and dose of past exposure, or the presence or absence of indices of metabolic disturbance. Some employ insensitive test methodology, or present other defects in research design.

Hopefully, new research will clarify some of the controversies over the "subclinical" effects of chronic low level lead exposure posed by the studies published so far on children. Some recent behavioral and functional studies in adults occupationally exposed to lead may also provide some insight to the problem. A recently released report by NIOSH based on 80 behavioral

measures of task performances and five measures of body lead burden in 316 lead workers and 112 controls, indicates that blood lead level is not a sensitive measure of changes in functional capacity, and that blood ALA-D is the most sensitive predictor of task performance. The study further indicates that intellectual functions are unaffected, while learning, neuromuscular and psychological functions are all influenced by body lead burden. (133)

In Experimental Animals

A number of recent experimental data in lower animals also provided some useful information. Silbergeld *et al.* demonstrated that exposure of suckling mice to lead from birth via mother's milk and water can produce developmental delays and hyperactivity, which responded paradoxically to the treatment with amphetamine and phenobarbitol, as is the case in hyperactive children. (134) Michaelson *et al.* similarly reported hyperactivity, aggressiveness, tremors and stereotype behavior in rats exposed since birth to lead in mother's milk and later in solid diet. These investigators further found a significant decrease in brain dopamine in exposed animals as compared to controls, suggesting a biochemical basis for the observed CNS dysfunctions. (136) Allen *et al.* found that early exposure to lead acetate produced hyperactivity and insomnia in infant rhesus monkeys, but not in adolescent and adult monkeys, despite findings of high blood lead levels and histopathological changes in liver and kidneys in the latter. These findings indicating greater vulnerability of the infant non-human primate to lead toxicity, are of considerable significance because of the implications in humans. (137) Carson *et al.* demonstrated slow learning of nonspatial, visual discrimination problems in 10-15 month old lambs exposed prenatally to only moderately increased maternal blood lead levels. None of the pregnant ewes showed clinical evidence of toxicity during or after the period of exposure. (138) This suggests that undue lead exposure at a "subclinical" level during pregnancy may cause subtle damage in the fetus. Recent studies by Fahim *et al.* indicated that undue lead absorption in pregnant women may in fact be associated with an increased incidence of premature rupture of membranes and premature delivery. (139)

WHAT OF THE FUTURE?

The issue of low level lead toxicity in children is far from clear-cut, but the implication of the many positive findings, both in humans and in lower

animals, is very grave. To date, screening programs in the U.S. have uncovered thousands of children with at least two blood lead readings of 40 μg/100 ml or more. Undue lead absorption in children has also been reported from other countries. There have been increasing indications in recent years that the upper limit of normal blood lead level set at 40 μg/100 ml may be too high, particularly for children and pregnant women, and should be revised to 30 μg/100 ml. (109,140) If the suggested limit is valid, the magnitude of the problem of undue lead absorption is actually many times the current estimate. Moreover, the interaction of lead with other metals and environmental pollutants such as cadmium, and mercury, also needs further clarification. Chelation therapy with its attendant undesirable side-effects and hazards should not be used indiscriminately. But, if chronic "low" level exposure to this potentially lethal element ubiquitous in our environment is in fact not totally harmless, with no systematic effort at preventing further undue exposure, what does the future hold for the thousands and thousands of children affected today, and the millions in the years to come?

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